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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/798,219	03/11/2004	Matilde Bustos De Abajo	U 015070-8	3487

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

MAIL DATE	DELIVERY MODE
09/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/798,219	ABAJO ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-19* is/are pending in the application.

4a) Of the above claim(s) *9-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 6/14/07 has been entered. The amendment to the specification is acknowledged. Claims 1-8 and 20-27 are canceled. Claims 9-19 are pending in the instant application. This application contains claims 9-11 drawn to an invention nonelected with traverse in the reply file don 9/6/06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 12-19 are currently under examination in the instant application. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in the previous office action.

Claim Objections

The objection to claims 12-19 and 27 is withdrawn in view of the amendments to these claims.

Claim Rejections - 35 USC § 112

The rejection of claims 12-27 under 35 U.S.C. 112, first paragraph, for lack of enablement is withdrawn over canceled claims 20-27 and maintained over amended claims 12-

19. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues that the specification clearly states the intended uses for the administration of CT-1 protein both as a prophylactic agent and a therapeutic to prevent or treat various types of liver damage by protecting cells from damage, i.e. apoptosis and necrosis, and/or inducing hepatic regeneration and provides adequate support and enablement based on common knowledge and the disclosed examples for the breadth of the claimed methods. Specifically, the applicant points to examples 9, 10, and 14 as providing sufficient enabling disclosure for the claimed invention. The applicant also discusses the relevance of the animal models used in the various working examples, citing a number of references as evidence that these models are art accepted as models of various types of liver damage.

In response, it is first noted that none of the references cited in the response are of record or have been provided to the examiner for consideration. Therefore, the teachings of these references cannot be evaluated. Regarding the teachings of the working examples, all of the working examples were fully considered in the preparation of the rejection of record. As noted in the previous action, the working examples all utilize the administration of a recombinant replication defective adenoviral vector encoding CT-1(Ad-CT-1), not a CT-1 polypeptide as claimed. Further, while the working examples do demonstrate that intravenous administration of Ad-CT-1 to various models can prevent liver damage through inhibition of apoptosis/necrosis caused by ConA, D-Gal and TNF alpha, or anti-Fas antibody, and also protect against apoptosis/necrosis in remaining liver tissue following subtotal liver resection, the working

examples are not correlative to the instant methods as claimed for reasons discussed in the previous office action and reiterated below.

First, the claims under examination are drawn to methods for stimulating hepatic regeneration comprising the administration of CT-1 polypeptide, claims 12-13, and 15-18, methods of preventing liver damage comprising administering CT-1 polypeptide, claim 14, and methods of treating an intrahepatic tumor comprising administering CT-1 polypeptide, claim 19. As can be seen, only claim 14 recites methods of preventing liver damage. The majority of the claims under examination recite methods for stimulating hepatic regeneration. However, while the working examples using Ad-CT-1 polypeptide do demonstrate inhibition of apoptosis/necrosis, nothing in the working examples demonstrates that the CT-1 expressed by the adenovirus stimulated hepatic regeneration after either subtotal hepatectomy or the administration of liver damaging agents. Further, as noted previously, the working examples teach the intravenous administration of Ad-CT-1, not CT-1 polypeptide. However, administration of Ad-CT-1 is not equivalent or correlative with the administration of CT-1 protein. Recombinant adenovirus has a natural tropism for the liver, such that intravenous injection can result in delivery of the vector to the target organ. CT- protein has no such tropism or targeting activity. Further, viral infection of hepatocytes results in transient continuous expression of the protein in the target cells for at least several days, if not longer, thereby reducing issues relating to protein half-life and clearance. Furthermore, dosages for the administration of adenoviral vectors and the dosages for protein administration are not comparable. The previous office discussed in detail that the specification provides no guidance concerning the dosage, the route of administration, or the number of protein administrations

required to achieve any therapeutic effect on hepatic regeneration or liver damage. Further, previous office action pointed out that the prior art teaches that intraperitoneal administration of CT-1 protein results in numerous effects on the host, including trophic effects on the heart, liver, thymus, and spleen, alterations in blood chemistry, and changes in platelets and red blood cells (Jin et al. (1996) Cytokine, Vol. 8 (12), 920-926). In view of the art recognized broad spectrum of effects of CT-1 protein administration, it would have required undue experimentation to determine the route of administration and amount of CT-1 protein capable of stimulating liver regeneration or preventing liver damage without causing potentially devastating side effects in other organ systems. Thus, the working examples using Ad-CT-1 do not provide an enabling disclosure for the administration of CT-1 polypeptide as claimed.

The previous office action also noted that the specification further fails to provide an enabling disclosure for treating chronic or acute liver diseases including hepatitis or cirrhosis by administering CT-1 protein. The prior art at the time of filing teaches that alcoholic hepatitis and cirrhosis are life-threatening diseases for which few treatments are currently available. While Narayanon Melon et al. teaches that stimulation of liver regeneration represents a future potential treatment approach for hepatitis and cirrhosis, Narayanon Melon et al. teaches that, "[t]his concept has been examined in patients with alcoholic hepatitis by treatment with insulin and glucagon, which is thought to stimulate liver regeneration. However, the results have been discouraging.", and that "[t]herapies using more selective hepatotrophic agents, such as hepatocyte growth factor, are compelling but remain untested.." (Narayanon Melon et al. (2001) Mayo Clinic Proceedings, Vol. 76 (10), 1021-1029, see page 1027). It is noted that CT-1 is not hepatoselective as it effects many organs and cells. Thus, the prior art at the time of filing

establishes that therapy of chronic liver diseases such as alcoholic hepatitis and cirrhosis by stimulating liver regeneration was considered unpredictable. Applicant's disclosure does not overcome the art recognized unpredictability for treating these diseases by stimulating liver regeneration as the specification does not provide any specifics as to protein dosage or administration or provide any evidence for therapeutic liver regeneration in patients with hepatitis or cirrhosis. Applicant's argument that the animal models tested in the working examples are art-recognized models of hepatitis and liver injury caused by chronic alcohol consumption also does not overcome the art-recognized unpredictability of stimulating hepatic regeneration in patients with these diseases as the working examples do not utilize CT-1 polypeptide administration and do not in fact demonstrate any level of hepatic regeneration induced by Ad-CT-1 in any of the models used.

Furthermore, the previous office action pointed out that the extent of the disclosure concerning the administration of CT-1 protein provided by the specification consists of a single mention of the use of CT-1 polypeptide on page 6, and the disclosure of a method of producing recombinant CT-1 protein in bacteria on page 9. The specification fails to provide any guidance regarding pharmaceutical compositions for the administration of CT-1 to patients, dosages of CT-1 which constitute an "effective amount" of CT-1 to prevent liver damage or stimulate hepatic regeneration, or routes of protein administration which are effective to deliver the protein to the liver. The specification further fails to provide any guidance as to the half-life of the protein under physiological conditions or teach the details of the treatment regimen for delivery of the "effective amount" of CT-1, i.e. a single dose of CT-1, or multiple doses on the same day or spread of several days. As such, the specification does not provide sufficient guidance for the

administration of an "effective amount" of CT-1 to achieve any of the claimed effects, including the prevention of liver damage, stimulation of hepatic regeneration, or treatment of intrahepatic tumors. Please note that the Federal Circuit has stated that:

> a specification need not disclose what is well known in the art. See, e.g., *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement.
> *Genentech Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1005 (CAFC 1997). (emphasis added).

Finally, the applicant has not addressed the grounds of rejection concerning the lack of enabling disclosure for treating intrahepatic tumors with CT-1. The previous office action stated that the specification is silent as to the treatment of intrahepatic tumors using CT-1. The only mention of tumors occurs on page 2, which states that cardiotrophin has been previously employed in the diagnosis and treatment of tumors, referencing WO 00/43790. However, this document in fact teaches away from using CT-1 protein to treat tumors. WO 00/43790 teaches that tumors, such as lung and colon tumors, overexpress CT-1 and discloses the treatment of these tumors by inhibiting CT-1 activity using antibodies against CT-1 and CT-1 antagonists (WO 00/43790, pages 2-3). As such, the prior art teaches the exact opposite of the instant methods as claimed and thus provides evidence of unpredictability for treating any tumor, including a hepatic tumor using CT-1. It is further noted that as the specification clearly teaches the anti-apoptotic activity of CT-1, the skilled artisan would not have predicted that an anti-

apoptotic protein would have any beneficial effect in killing tumors cells or in inhibiting their growth. Thus, due to the anti-apoptotic properties of CT-1, the teachings of the prior art to inhibit CT-1 activity to treat tumors, and the complete lack of guidance in the specification for using CT-1 to treat intrahepatic tumors, it would have required undue experimentation to practice the methods of treating tumors as claimed.

Therefore, for reasons of record as discussed in detail above, the rejection of claims 12-19 stands.

Claim Rejections - 35 USC § 102

The rejection of claims 12, 14, 20, and 22 under 35 U.S.C. 102(b) as being anticipated by Jin et al. (1996) Cytokine, Vol. 8 (12) 920-926, is withdrawn over canceled claims 20 and 22 and maintained over amended claims 12 and 14. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues that Jin et al. does not teach each and every element of the claimed invention as required for anticipation. Specifically, the applicant argues that Jin et al. does not teach that the administration of CT-1 protein prevents liver damage of stimulates hepatic regeneration. This argument, however, is not found persuasive. The rejection of record stated, " .. while Jin et al. does not specifically teach that the administration prevents liver damage, the method steps taught by Jin et al. for inducing liver growth are identical to those claimed. The applicant is reminded that merely discovering and claiming a new benefit to an old process cannot render the process again patentable. *In re Woodruff*, 919 F. 2d 1575, 1577-78, 16

USPQ2d 1934, 1936-37 (Fed.Cir. 1990); *In re Swinehart*, 439 F.2d 210, 213, 169 USPQ 226, 229 (CCPA 1971); and *Ex Parte Novitski*, 26 USPQ2d 1389, 1391 (Bd. Pat. App. & Int. 1993)".

As discussed in section 2112.02 of the MPEP, the Board in *Ex Parte Novitski* rejected a claim directed to a method for protecting a plant from plant pathogenic nematodes by inoculating the plant with a nematode inhibiting strain of P. cepacia. A U.S. patent to Dart disclosed inoculation using P. cepacia type Wisconsin 526 bacteria for protecting the plant from fungal disease. Dart was silent as to nematode inhibition but the Board concluded that nematode inhibition was an inherent property of the bacteria. The Board noted that applicant had stated in the specification that Wisconsin 526 possesses an 18% nematode inhibition rating. See also *In re May*, 574 F.2d 1082, 1090, 197 USPQ 601, 607 (CCPA 1978), which states that when the claim recites using an old composition or structure and the "use" is directed to a result or property of that composition or structure, then the claim is anticipated. Regarding *In re May*, Section 2112.02 of the MPEP states that in this case, "Claims 1 and 6, directed to a method of effecting nonaddictive analgesia (pain reduction) in animals, were found to be anticipated by the applied prior art which disclosed the same compounds for effecting analgesia but which was silent as to addiction. The court upheld the rejection and stated that the applicants had merely found a new property of the compound and such a discovery did not constitute a new use". The process of administering CT-1 protein is clearly and specifically taught by Jin et al. As such, Jin et al. anticipates the instant claims.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your

application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633